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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STUCKER, JEFFREY J	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,534	ENSOLI, BARBARA	
	Examiner	Art Unit	
	Jeffrey Stucker	1648	

-- The MAILING DATE of this communicati n appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-72 and 76-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-72 and 76-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *25* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/6/03 has been entered. Claims 62-72 and 76-88 are pending and under final rejection.

Amended claim 67 is objected to for a typographical error. The last line, the "is" should be "its".

The new figure 1 is accepted.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The rejection of claims 62-72 and 76-81 under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks patentable utility is withdrawn.

The rejection of claims 62-72, 76-81, and new claims 82-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing an immune response, does not reasonably provide enablement for vaccines for treating or preventing HIV related disease is maintained and applied to new claims 82-88 as the same rational is applicable to the new claims.

Applicant's arguments have been fully considered but are not deemed to be persuasive. Applicant argues that monkey models are valid models for human therapy, the claims to a vaccine for HIV are fully enabled, and the specification provides sufficient guidance to one of ordinary skill in the art to overcome unpredictability.

Applicant has provided numerous references to support an argument that the macaque model disclosed in the instant specification is an accepted model for testing the efficacy of hoped-for HIV vaccines. The references provided in the response and cited on the form 1449 filed concurrently have been carefully reviewed.

BH notes in the first paragraph, in reference to non-human primate experiments, that the same data has failed to convince the vaccine manufacturers to take these vaccine candidates into human clinical trials on their own budget. The last section of

the paper, "A Human Efficacy Trial Has to Be Carried Out in Parallel", teaches that human testing of vaccine candidates will determine if testing HIV-1 vaccines in non-human primates has any value in the developments of an effective vaccine. Neither of these statements is calculated to convey that results gained the macaque model are transferable to humans. In deed, the last statement clearly indicates that non-human primate models have yet to be validated for human vaccines.

BL discloses that research has been done with SIV in macaques. While the first column states that many observations in monkeys have been confirmed in man, this does not say that vaccines in monkeys have been successful in man. In a telling passage in the last paragraph of the paper, under "conclusion", it states that "[u]ltimately, only phase 3 efficacy trials in humans will establish if the modest protection induced by subunit vaccines is sufficient to alter the course of the AIDS pandemic."

BI and BM are cited to show that CTLs are protective. Though BI teaches that CTLs in the acute phase of infection are inversely related to viral levels, it also teaches on the first page, second column, that the CTL response ultimately fails to control HIV, unlike other chronic viruses that are controlled by CTLs. BM discloses a long term nonprogressor that has a strong

CTL response. The introduction teaches that CTL responses are important but it also teaches that a strong antibody response is important. Further, there are many factors that can be responsible for protection from disease. It is clear from the article that the subject is infected with a replication defective virus with no indication that this was the result of CTLs.

BK is cited to show that the tat of the reference did not provide protection and is different than the instantly claimed tat because there is no discussion in the reference as to how the protein was purified. Of course, this does not indicate that it was not oxidized or aggregated. The reference indicates that, give the apparent lack of success with "biologically active" tat, the protein and methods of using it, at the least, are critical and unpredictable.

BA was cited to show that the authors cautioned readers in interpreting the results of this experiment since the rhesus monkeys were challenged with a highly pathogenic clone and the study was not designed to induce CD4 T-cell responses. This reference is irrelevant as the monkeys were infected with SIV, not HIV or even SHIV.

Though the SHIV/macaque model is often used in HIV studies, it does not follow that one of ordinary skill in the art would

reasonably expect the same positive results in humans, as indicated in the excerpts from applicant's references.

Administering tat by administering DNA encoding tat to humans, though inducing CTLs, does not provide any degree of protection. Applicant asserted on page 22, second paragraph, of the response that tat cDNA has been shown in humans to induce protective immune responses. This is clearly not supported by the references cited by applicant. References of particular interest in this regard were cited by applicant as BC and BD. Applicant asserts that these articles teach that tat cDNA induces protective immune responses against HIV-1 tat in humans. This is in contrast to what is stated in the articles themselves. BC directly contradicts applicant's assertion. One need look no further than the abstract: "The DNA immunization induced Ag-specific T cell proliferation, which persisted up to 9 mo after the last DNA injection, and cytolytic activities but did not, by itself, reduce viral load." It is quite clear from a fair reading of the text that any reduction in viral load was due to HAART, not CTL activity. BD teaches only that T cell activity can be induced and specifically states in the penultimate paragraph that there is "no evidence of a decreased viral load."

BJ is another reference which is a review of various animal models that are used in the study of HIV. The authors conclude that it is unclear that either the chimpanzee or macaque models compare with humans and HIV infection. See the last paragraph.

Additional articles not cited by applicant are also relevant. Feinberg et al. state in the last paragraph that, though the macaque models can potentially add important insights, "[a]nimal models cannot determine whether a vaccine will be effective against HIV-1 infection of humans; only Phase III trials in humans can do so." Even applicant's own published work on the subject matter of the instant claims teaches that one does not know how to make and use the disclosed vaccine as a method of preventing infection. See page 647, second column of Cafaro et al.: "However, the immune response against Tat cannot block virus entry."

Applicant argues that the instant invention is enabled because the specification teaches how to purify a "biologically active tat". This is not convincing as the scope of the invention exceeds merely a biologically active tat. The specification does not teach how to make and use a biologically active tat anti-HIV-1 vaccine. As demonstrated above, merely having a biologically active tat, even if it does provide some

degree of protection in macaques, does not teach that it is an anti-HIV-1 vaccine.

Given the uncertainty in the vaccine art as demonstrated by the references and the lack of relevant working examples in the instant specification, the instant application lacks sufficient guidance to overcome unpredictability for vaccines.

The rejection of claims 62, 65-68, 72, 76, and 79 under 35 U.S.C. § 102(a) as being anticipated by Frankel et al. (5,652,122) is withdrawn in view of the teachings of Frankel et al. in column 9, that the present invention removes the cysteine-rich region which eliminates the induction of HIV activation.

The rejection of claims 62, 63, 69, 77, and 78 under 35 U.S.C. § 103(a) as obvious over Frankel et al. is withdrawn in view of the teachings of Frankel et al. in column 9, that the present invention removes the cysteine-rich region which eliminates the induction of HIV activation.

On multiple occasions during the weeks of January 6-24, 2003, the examiner indicated allowable subject matter to applicant. Specifically, the necessary action required to place the application in condition for allowance are:

remove "vaccine" and intended use from the claims,

clarify the structure of the tat i.e., non-aggregated and non-oxidized as per the arguments.

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The

faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

The Group 1600 Fax number is: (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Stucker whose telephone number is (703) 308-4237. The examiner can normally be reached Monday to Thursday from 7:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JEFFREY STUCKER
PRIMARY EXAMINER